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PRINCIPAL INVESTIGATOR: Joseph B. Long, PhD

CONTRACTING ORGANIZATION: The Geneva Foundation Tacoma, WA 98402

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| 13. SUPPLEMENTARY NOTES | | | | | |
| 14. ABSTRACT The etiology of blast-induced traumatic brain injury (bTBI) is largely undefined. Along with reducing mortality, in preliminary experiments Kevlar vests significantly protected against bTBI in rats. We postulate that: 1) blast-induced fiber degeneration in brain results from pressure surges transmitted through the vasculature that elicit intracranial disruptions, and 2) Kevlar vests are neuroprotective by uncoupling this pressure transmission following exposure to blast. Using a compression driven shock tube, we compare external, systemic (e.g. vascular), and central (e.g. intracranial pressure) BOP-induced pressure changes, and assess the impact of Kevlar vests on these changes. We seek to: 1) determine if measured pressure changes are blast severity-dependent and correspond with outcome measures, and 2) assess the impact of Kevlar vests on measured BOP-induced pressure changes and outcome measures and establish whether a protective vest encasing the thorax ameliorates blast-induced brain injury, pointing to a contribution of the effects of blast on the thorax to brain injury. These studies will provide insights into the etiology of blast-induced brain injury and will advance the development of mitigation strategies. | | | | | |
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Table of Contents

| | |
|------------------------------------|---|
| INTRODUCTION..... | 4 |
| BODY..... | 4 |
| KEY RESEARCH ACCOMPLISHMENTS | 6 |
| REPORTABLE OUTCOMES..... | 7 |
| CONCLUSION | 7 |
| REFERENCES..... | 7 |
| APPENDICES | 7 |

INTRODUCTION

Body armor has made blast injuries survivable; consequently, we speculate that to a large extent blast-induced head injuries have emerged among troops who without body armor would have simply been killed in action as a result of injury to more vulnerable organs such as the lung. Serendipitously, in a preliminary experiment we noted that along with reducing mortality, lung injury, and cardiovascular disruptions by blast overpressure (BOP), Kevlar vests protected against BOP-induced neuropathological changes in rats. These preliminary findings suggested that a protective vest encasing the thorax might ameliorate blast-induced brain injury, pointing to a significant contribution of the effects of blast on the thorax to brain injury pathophysiology. We hypothesize that much of the blast-induced fiber degeneration in brain results from pressure surges transmitted through the vasculature (venous as well as arterial) that elicit a series of intracranial disruptions, and that Kevlar vests are neuroprotective by uncoupling this pressure transmission following exposure to blast.

To address how BOP effects on the thorax contribute to brain injury and to evaluate how Kevlar vests protect the brain, we are attempting to measure, compare, and correlate external, systemic (e.g. vascular arterial and venous), and central (e.g. intracranial pressure) BOP-induced pressure changes, and assess the impact of Kevlar vests on these changes. In particular, we use a compression driven shock tube to: 1) determine if measured pressure changes are blast severity-dependent and correspond with neuropathological and neurobehavioral outcome measures, and 2) assess the impact of Kevlar vests on measured BOP-induced pressure changes and outcome measures. As detailed below, in addition to neuropathological and neurobehavioral evaluations, these outcome measures include assessments of blood-brain barrier integrity and cerebral blood flow measurements, since we postulate that the cerebrovasculature plays a pivotal role in blast-induced brain injury pathophysiology, and is likely to be disrupted by blast-induced perturbations.

BODY

An air-driven shock tube has been used to simulate blast overpressure (BOP) and study how BOP effects on the thorax contribute to brain injury and to evaluate how Kevlar vests protect the brain. We have generally completed the work outlined in the progression of milestones for this project as was described in the previous annual report. We requested a NCE continuation period to prepare reports and manuscripts, and to also replicate experiments using a recently acquired advanced blast simulator (ABS, fig 1) which provides a substantial refinement and improvement over the open-ended cylindrical shock tubes generally used for laboratory blast simulations. Working closely with Dave Ritzel, a blast physics expert, we became aware of several

drawbacks of the cylindrical shock tube used for all experiments with this project to-date, which are true for all open-ended cylindrical shock tubes; notably, in the absence of an end wave eliminator, the negative phase and recompression waves are artefacts of the rarefaction from the end of the open tube and the secondary shock is moving in the reverse direction (upstream not downstream). Additionally, without a reflection eliminator, waves reverberate throughout the length of the tube after the passage of the initial shock front (Ritzel et al., 2011). Finally, rather than the sharp peak positive pressures associated with the Friedlander waveform, cylindrical shock tubes typically produce plateau waveforms with relatively long durations (6-12 msec). With a divergent transition section and an end wave eliminator, the recently acquired ABS eliminates these artefacts along with much of the variation in pressures encountered as one moves from the axial center of the tube to the walls. Positive pressure durations can be reduced to 1-2 msec. While the work on this project has been substantially completed using the cylindrical shock tube, we think it will be valuable to repeat several key experiments using the new ABS to confirm results, particularly since the means by which rats were secured in the old shock tube and exposed to blast overpressure evolved over the duration of the project. Confirmation of these results following refinement of the fidelity of our blast simulation in the ABS will validate the findings and also provide valuable insights for their interpretation. In particular (and as noted previously), working closely with Dave Ritzel, we modified both the holder and the positioning of the rat in the cylindrical shock tube over the course of this project, specifically exposing anesthetized rats to a shock wave while snugly suspended in a tautly drawn course mesh netting 2.5 ft within the tube. These modifications moved the experimental subject away from collimated jet exit flow conditions at the mouth of the shock tube and also reduced displacement and substantial acceleration otherwise occurring with a less secured subject. As a result of these “cleaner” improved BOP exposure conditions, TBI severity diminished as also did the functional impairments resulting from BOP exposure. As a consequence, it became difficult documenting persistent neurobehavioral deficits after BOP exposures, despite attempts to improve the sensitivities of these tests to distinguish mild TBI. When a back-ordered rat holder for the ABS is installed, we will be able to further address hypotheses under further improved high fidelity blast exposure conditions. Bad blast simulations have confounded much of the preclinical biomedical blast literature to date, and we strongly desire to reverse that situation.

Task 1: Using a compression-driven shock tube, measure, compare and correlate external (i.e. shock tube), systemic (i.e. vascular arterial and venous), and central (e.g. intracranial pressure) effects of BOP of varied intensities.

As noted in our last report, using rupturable Mylar membranes of varied thicknesses, we mapped the cylindrical shock tube using tip and side-on gauges to provide total and static pressure measurements throughout its length. More recently, we have used

identical gauges to record shockwave pressures in the new ABS (fig 2). The divergent transition section design of the ABS yields shock waves of shorter duration which are followed by a negative pressure, much more closely resembling Friedlander waveforms encountered in the open field. We have experimented and evaluated the pressure waveforms produced with different membrane materials (e.g. Mylar vs acetate) and different gases (e.g. compressed air vs helium). With incorporation of a rat holder in the ABS, we will next evaluate systemic (i.e. vascular arterial and venous), and central (e.g. intracranial pressure) effects of BOP of varied intensities in the ABS.

Task 2: Determine if measured pressure changes in the experimental subject are blast severity-dependent and correspond with neuropathological and neurobehavioral outcome measures.

While awaiting a rat holder for the ABS, we have explored EEG changes as an outcome measure to accompany other neurobehavioral assessments. Based upon work with other experimental brain injury models, initial efforts focused on seizure events and epileptiform activity. However, seizures and epileptiform activity have proven to be much less prominent, reproducible, and lasting in experimental subjects following blast exposures, so we have redirected EEG evaluations to assess other characteristic changes resulting from blast exposure. In particular, algorithms have been developed to perform power spectral analyses and evaluate changes in the delta frequency (0-4 Hz) relative to all other frequencies recorded (i.e. total power of the spectra) over 30 days post-blast.

Task 3: Assess the impact of Kevlar vests on measured BOP-induced pressure changes and neurobehavioral outcome measures.

We have not done additional work with Kevlar vest evaluations during this reporting period, and will do so when rats are exposed to blast in the new ABS.

Task 4: Assess the impact of Kevlar vests on measured BOP-induced pressure changes and acute cerebrovascular measurements.

We have not done additional work with Kevlar vest evaluations during this reporting period, and will do so when rats are exposed to blast in the new ABS.

KEY RESEARCH ACCOMPLISHMENTS

- With acquisition of an advanced blast simulator (ABS), BOP exposure conditions have been further characterized and refined to create a high fidelity simulation of blast TBI.
- BOP-induced acceleration and displacement were discovered to present potentially significant contributions to TBI injury mechanisms in the cylindrical

shock tube and are being recorded and controlled for BOP exposures in the ABS.

- EEG assessments have been further developed as a means of characterizing blast TBI and amelioration of blast TBI by protective vests.

REPORTABLE OUTCOMES

No additional abstracts or publications were submitted during this reporting period. Based in part upon the work supported by this award, funding was sought through research pre-proposals and proposals submitted to the CDMRP and DMRP.

CONCLUSION

An improved state-of-art high fidelity laboratory simulation of blast has been achieved using an advanced blast simulator (ABS) and pressure gauges record the static and dynamic pressures specifically occurring in the immediate environment of the experimental subject for each shockwave. From these measurements, wave velocity and dynamic pressure (blast wind) can be calculated. Following these characterizations, the ABS will now be used to validate findings made with a cylindrical shock tube in which intracranial and intravascular pressure recordings closely resembled ambient pressures and were unaltered by protective vests..

REFERENCES

Ritzel, D.V., Parks, S.A., Roseveare, J., Rude, G. Sawyer, T., "Experimental Blast Simulation for Injury Studies", NATO/RTO HFM-207 Symposium, Halifax, Canada, 3-5 Oct 2011.

APPENDICES

1. Supporting Data

SUPPORTING DATA

During this reporting period, a 24 in diameter advanced blast simulator (ABS) has been installed at WRAIR (Figure 1) and generates shockwaves with much higher fidelity to the Friedlander waveforms produced by explosives in the open field (Figure 2). In particular, with its divergent transition section and end wave eliminator, the ABS waveforms contain a genuine negative pressure phase and a secondary shock in contrast to pressures recorded in cylindrical shock tubes (Figure 3). In addition, the shorter wave duration is better scaled to IED explosions.

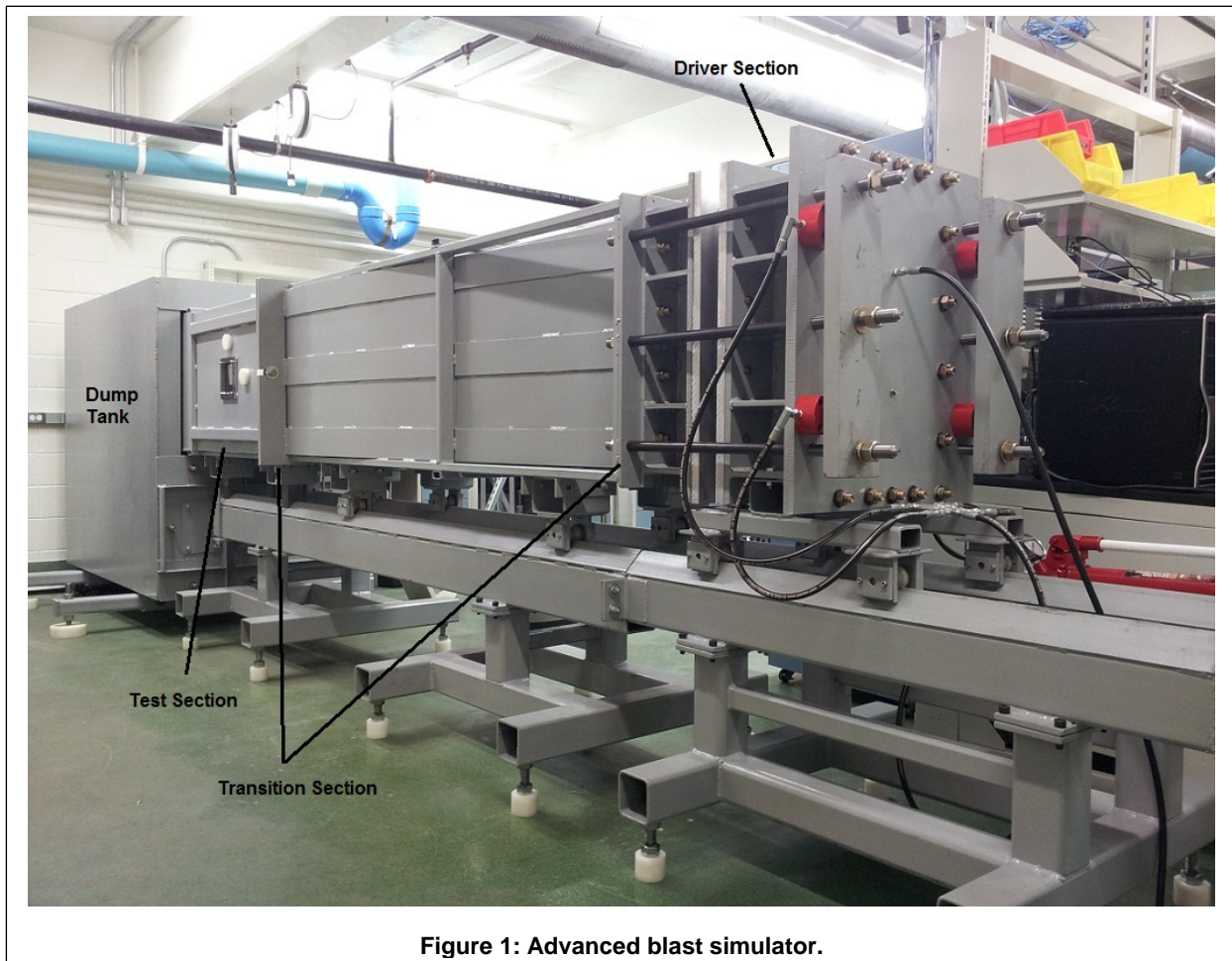


Figure 1: Advanced blast simulator.

The ABS overcomes several other limitations of conventional open-ended cylindrical shock tubes, in which the negative pressure phase and recompression waves are artefacts of the rarefaction from the end of the open tube and the secondary shock is actually moving in the reverse direction (upstream not downstream). In addition, the end wave or reflection eliminator prevents wave reverberation otherwise occurring throughout the length of the tube (Figure 4).

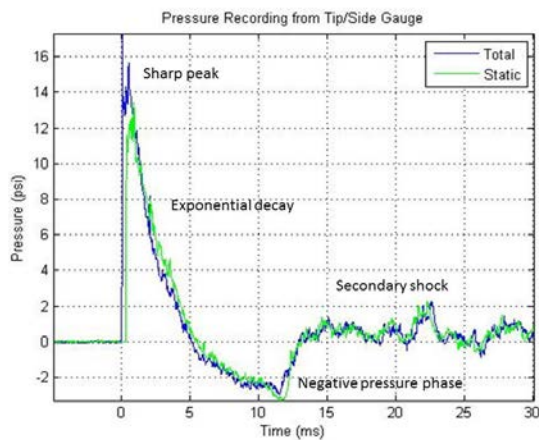


Figure 3: ABS pressure trace

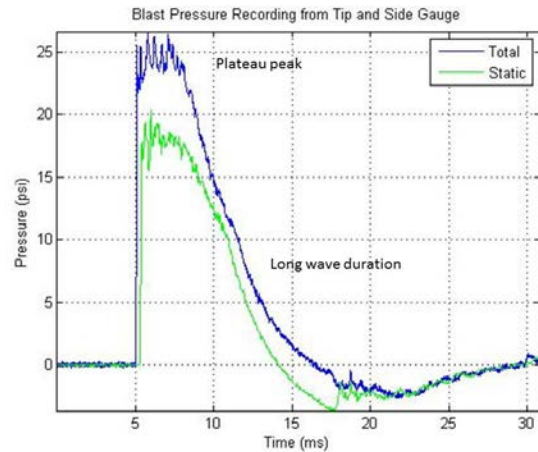
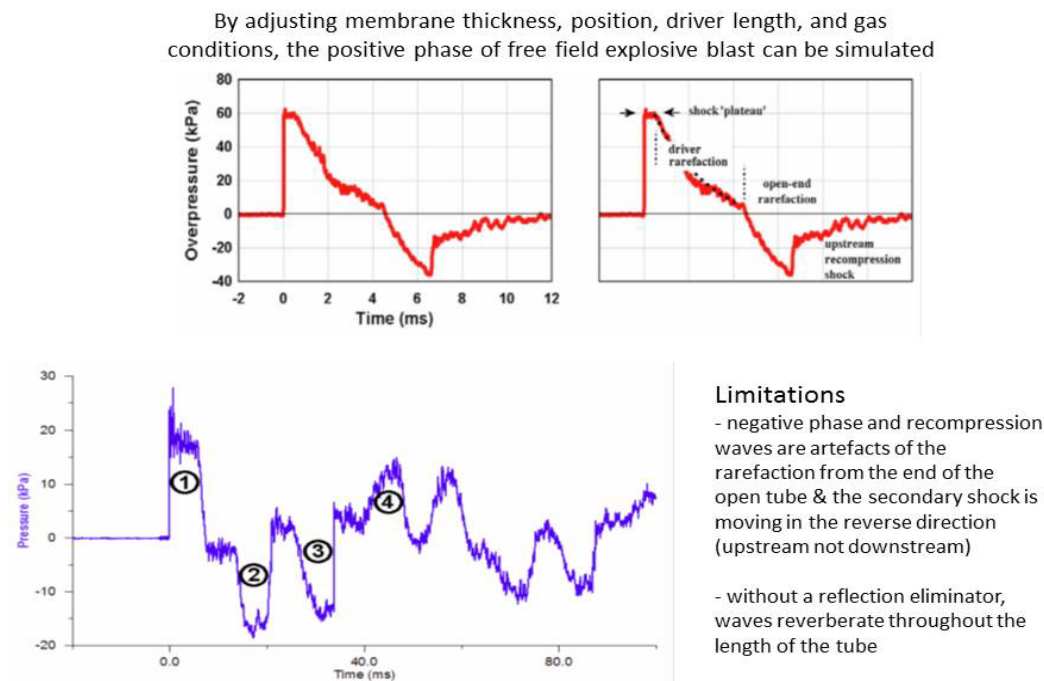


Figure 4: Cylindrical shock tube pressure trace

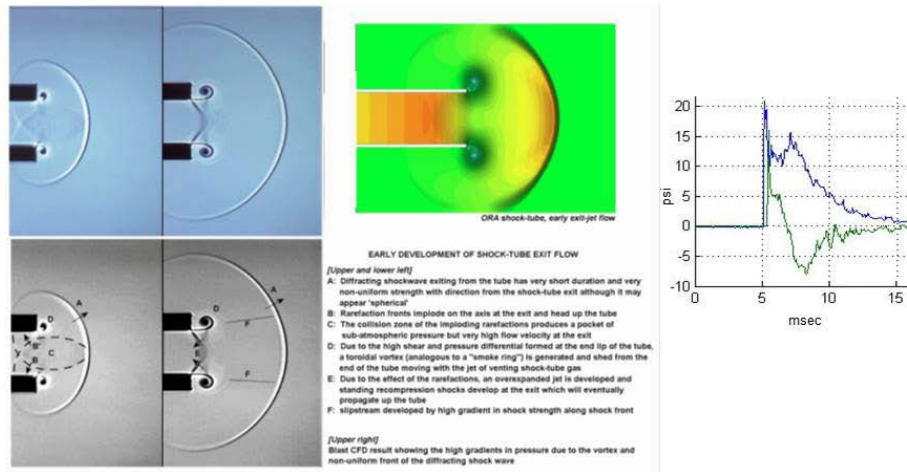
Another too-frequent cause of artefact is positioning test subjects immediately outside the mouth of the shock tube; flow conditions are unstable and complex involving development of an 'end-jet' with high flow gradients such that slight variations in position impart large changes in static and dynamic pressure conditions (Figure 5). Positioning of test subjects within a well characterized test section of the ABS avoids many of these confounding causes of misinterpreted data.



From: Ritzel DV et al., Experimental blast simulations for injury studies. NATO RTO-HFM-207, 2011.

Figure 2

Position subject in the tube, not outside the mouth of the tube



From: Ritzel DV Basics of Blast Physics and Simulation for Injury Studies Short Course, Nov 2013

Figure 6

As noted above, in addition to improving the fidelity of blast simulations, during this reporting period we have also refined EEG analyses to better evaluate functional brain disruptions resulting from blast and improvements associated with vest protection. Telemetric cortical EEG recordings are made using DSI transmitters; EEG is recorded continuously during a 48 hr preinjury baseline period, during blast exposure, and during a 2 week postinjury phase. In these pilot experiments, shifts in delta activity have replaced seizures and epileptiform activity as the basis for EEG analysis (Figure 6).

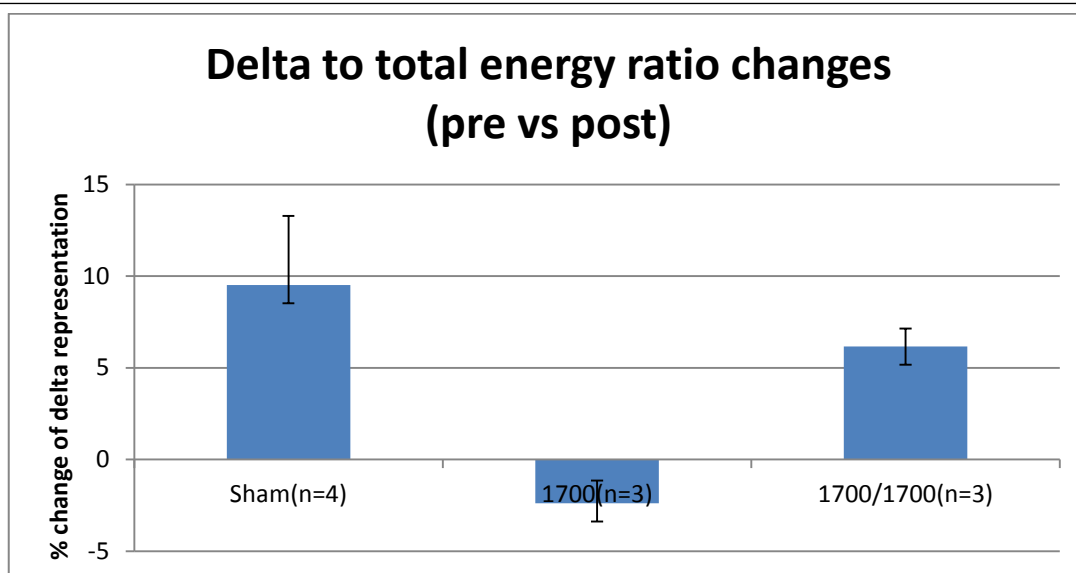


Figure 5